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EXAMINER	
CARLSON, K	
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DATE MAILED: 05/24/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☑ Responsive to communication filed on 10-11-94 (#15) ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), - days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 2-7, 9-14, 17, 18, 22, 23 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1, 8, 24-26, 15, 16, 19-21 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 2-7, 9-14, 17, 18, 22, 23 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☒ been received ☐ not been received ☐ been filed in parent application, serial no. 07/571430 ; filed on 4-20-90.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

The instant application is a FWC of 08/153287. Claims 1, 8, and 24-26 have been cancelled. Claims 2-7, 9-14, 17, 18, 22, and 23 are currently pending and under examination.

This Office Action addresses arguments made in Paper #15, filed October 11, 1994, as these arguments pertain to the rejection below.

Claims 7, 13, 14, 18, and 23 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to DNA encoding the TNF-BP described as R^2-Asp-Ser-Val-.... See M.P.E.P. §§ 706.03(n) and 706.03(z). Claim 7 is directed to DNAs that hybridize to the DNA encoding TNF-BP identified in Claim 2 and encoding a protein that can bind to TNF. This DNA is beyond the scope of the disclosed Invention because there is no teaching in the specification what part of the TNF-BP is responsible for binding to TNF. It is not predictable what part of TNF-BP binds to TNF because no structure/function studies have been done such that one of ordinary skill in the art could know that part of the TNF-BP encoded by the DNA of Claim 2 will retain TNF binding function. Therefore, it would require undue experimentation for one of ordinary skill in the art to determine that part of the TNF-BP encoded by the DNA of Claim 2 that is responsible for TNF binding.

Claim 13 is directed to any DNA encoding any TNF binding protein. The specification is non-enabling for the scope of the claimed binding proteins because the disclosure is not commensurate in scope with the Claims for the breadth of the various kinds of TNF binding proteins obtainable. This is particularly emphasized because the specification has only taught the preparation and activity of one TNF binding protein is Asp-Ser-Val-... A binding protein can be an antibody directed against TNF, for example, or the extracellular domain of undisclosed TNF receptors. There is no guidance provided in the specification as to how one of ordinary skill in the art would

obtain these TNF binding proteins. Therefore, it is not predictable what comprises the TNF binding protein because their composition and relative function can be as varied as an antibody or a ligand binding domain of a receptor. Additionally, these binding protein can antagonize TNF action at its receptor or they can prolong the half-life of the TNF; therefore, it is not predictable what the outcome of TNF binding by these undisclosed binding proteins will be. In essence, the Claims encompass several different binding proteins for which there is insufficient enablement. *In Ex parte Hitzman* (9 USPQ 2d 1821), the courts have re-emphasized that "more will be required in cases that involve unpredictable factors, such as most chemical reactions and physiological activity." It would require undue experimentation to predict and prepare the binding proteins encompassed within the scope of the Claims that possess the desired and favorable characteristics set forth in the specification, in the absence of sufficient information to predict the results with an adequate degree of certainty (*Ex parte Forman*, 230 USPQ 546).

Claims 13, 14, 18, 23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 is directed to recombinant DNA capable of replicating in a host cell. It is not clear if this DNA is a vector comprising cDNA encoding a TNF binding protein or the cDNA encoding a TNF binding protein because no references is made to expression control sequences, for example. This Claim should be amended to more succinctly describe the vector or the cDNA encoding the TNF binding protein.

Claim s 3-5 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject

matter of a previous claim. Claims 3-5 depend from Claim 2 wherein the R^2 is optionally present or absent. When R^2 is absent, the R^2 of Claims 3-5 do not further limit the sequence depicted in Claim 2.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Abbreviations: TNF-BP = tumor necrosis factor binding protein

TNF-R = tumor necrosis factor receptor

GH-BP = growth hormone binding protein

GH-R = growth hormone receptor

Claims 2-7, 9-14, 17, 18, 22, and 23 are rejected under 35 U.S.C. § 103 as being unpatentable over Olsson et al. (March, 1989) in view of Leung et al. (December, 1987). Olsson et al. teach the isolation of TNF-BP from urine (page 271 to page 272). This binding protein successfully competed with ^{125}I-TNF for binding to HL-60 cells (page 271, col. 2, top; page 274, col. 1). The N-terminal amino acid sequence of the TNF-BP was determined to be (page 272, col. 2):

Asp-Ser-Val-X-Pro-Gln-Gly-Lys-Tyr-Ile-His-Pro-Gln-Val-Asn-Ser-Ile-X-Lys-Thr

Olsson et al. conclude that it would be of considerable importance to investigate the possibility that TNF-BP could neutralize the harmful effects of TNF *in vivo*. Olsson et al. also state that "In addition it is important to

consider the possibility that the TNF-BP may be the soluble form of the TNF receptor" (page 275, col. 1). Olsson et al. do not teach the cDNA encoding the TNF-BP or the signal sequence for its secretion.

Leung et al. teach the relationship of GH-BP and GH-R. Leung et al. purified both the GH-R (page 538) and the GH-BP (page 539) and found that the N-terminal amino acid sequence for both of the protein were the same (Table 1; page 540, col. 2). Leung et al. concluded that the serum binding protein is the extracellular hormone binding domain of the membrane bound GH-R (page 538, col. 1, para. 2; Page 541, col. 1). GH-R clones were isolated by first screening liver (which expresses GH-R) cDNA libraries with a 57 mer oligonucleotide probe based on the 19 amino acid sequence of a tryptic fragment of the receptor (page 541, col. 1; Table 1 and legend) and then rescreening the same libraries with fragment probes obtained from the initial set of clones (page 541, col. 2, top). The complete cDNA and amino acid sequence encoding the GH-R are shown in Fig. 3. The N-terminal amino acid sequence is preceded by 18 amino acid signal sequence identified by the Met initiation codon and 14 hydrophobic amino acids flanked by charged residues (page 542, col. 1). A hydropathy plot of the GH-R amino acid sequence shows one major hydrophobic region of 24 amino acids in the center of the sequence which separates the extracellular, N-terminal, GH binding domain from the intracellular, C-terminal, signalling domain (page 542, col. 1).

The full-length GH-R sequence was assembled in a mammalian expression vector under the control of the CMV promoter and transiently transfected into COS-7 monkey kidney cells wherein the GH-R was expressed on the membrane as evidenced by ^{125}I-GH binding (page 542, col. 2 to page 543, col. 1). A stop codon was placed at the first amino acid of the transmembrane domain (position 247) and this DNA encoding the signal sequence and the extracellular domain of the GH-R was placed in the same vector used for the expression of GH-R (page

543, col. 2). COS-7 cells were transiently transfected with this vector and the extracellular domain was secreted into the culture medium. The GH-BP was shown to have high affinity for GH. Leung et al. conclude that the purification and protein sequence data established the structural identity of the GH-BP as the extracellular hormone binding domain of the GH-R.

It would have been obvious to a person of ordinary skill in the art to acquire the cDNA encoding the TNF-BP described by Olsson et al. using the method of Leung et al. with obvious modifications of the method directed to the particulars of the TNF-BP because Olsson et al. teach that the TNF-BP may be the extracellular domain of the TNF-R and Leung et al. teach this method in which GH-BP was identified as the extracellular domain of the GH-R. To this end, it would have been obvious to a person of ordinary skill in the art to screen HL-60 cDNA libraries with oligonucleotide probes encoding the N-terminal sequence of the TNF-BP to obtain cDNA encoding the full-length TNF-R because Olsson et al. teach that the TNF receptor expressed in HL-60 cells because TNF binds to these cells and that the TNF-BP may be the extracellular domain of the TNF-R. It would have been obvious to a person of ordinary skill in the art to produce a hydropathy plot of the amino acids encoded by the DNA obtained to determine the signal sequence and transmembrane domain of the TNF-R because Leung et al. teach this method to identify the signal, extracellular, transmembrane, and intracellular domains of the GH-R. It would have been obvious to a person of ordinary skill in the art to place the cDNA encoding the TNF-R into a mammalian expression vector and transfect mammalian cell lines to express the receptor to demonstrate that the TNF-R is TNF-specific as taught by Leung et al. for the GH-R. Specific to the claimed invention, because Olsson et al. teach that the TNF-BP is likely the extracellular domain of the TNF-R, it would have been obvious to a person of ordinary skill in the art to identify the cDNA encoding the extracellular

domain of the TNF-R (Claims 2, 7, 13) and place a stop codon at the amino acid position of the hydropathy plot-identified transmembrane domain to prevent the expression of the TNF-R and place the signal sequence (Claims 3-6) and extracellular binding domain (Claims 2, 7, 13) in an expression vector (Claims 9-14) and express the signal sequence and extracellular domain/TNF-BP in a mammalian cell line (Claims 14, 17, 18) to demonstrated that the protein produced secreted is a TNF-BP (Claims 22, 23) like Leung et al. did for the identification of the GH-BP. The specific plasmids of Claims 11 and 12 do not appear to functionally differentiate from that of Leung et al. Therefore, these plasmids are considered to be obvious over the prior art.

Additionally, even if the TNF-BP were found to be separate and distinct from the TNF-R, as is possible as taught by Olsson et al., one of ordinary skill in the art would reasonably expect to successfully obtain the cDNA encoding the secreted TNF-BP because the N-terminal amino acid sequence provides oligonucleotide probe information necessary to carry out the cloning of the TNF-BP in and of itself, using the method of Leung et al.

Response to Paper #15

The Examiner will respond to only those arguments that appear to be specific to the rejection above, especially because most of the arguments are directed against Wallach 1.

Applicants arguments as a whole appear to be directed to matters of routine experimentation in cloning. Applicants argue (page 3) that nowhere in the cited art is there a teaching of which cDNA library to choose. This argument is moot because Olsson et al. show that TNF-Rs are expressed on HL-60 cells and, given the emphasis on the TNF-R, cDNA libraries to be screened will be those expressing TNF-R, that is, that respond and or bind to TNF like TNF-sensitive cell lines, for example.

Applicants note that Wallach 2 use two cDNA screens, the second probes deriving from the partial clones obtained by the degenerate primers. The use of two or more screens is routine in the art because one can increase the specificity of the hybridization to the cDNA of interest more quickly obtain the full-length cDNA using a longer probe having the DNA sequence encoded by the cDNA libraries. This argument is considered to be moot in light of the citation of Leung et al. who demonstrate this procedure for the acquisition of cDNA encoding GH-R.

Applicants state on page 8 that the cDNA encoding the TNF-R would be obtained using the routine methods and not cDNA encoding only TNF-BP because no discrete mRNA encodes the soluble TNF-BP. The inclusion of Leung et al. in the art rejection above provides a basis for different domains within a receptor to identify the binding protein and therefore renders this argument moot. As noted above, even if the TNF-BP is distinct from the TNF-R, this method using the cDNA encoding the N-terminal amino acids as degenerate primers would be expected to isolate the cDNA encoding the TNF-BP.

Applicants argue that the rejection is based on an "obvious to try" standard. The Examiner disagrees because the information needed to clone the TNF-BP/TNF-R is provided in Olsson et al. as well as substantial motivation to do so. All one had to do was to "plug in" these variables into the method of Leung et al. to successfully clone the TNF-R and derive the TNF-BP therefrom.

Applicants cite *In re Bell* and state that the Examiner should not reject the composition claims in light of generic methods, and especially in light of the disclosure of Wallach 2. The Examiner is not convinced that the DNA encoding the TNF-BP is not obvious because not only was a substantial part of the N-terminal sequence of the TNF-BP known, Olsson et al. also set forth that the TNF-BP may be the binding domain of the TNF-R. Cloning procedures are art-recognized and any minor alterations such as primer degeneracy and so

forth are not considered to be undue experimentation.

The Examiner believes that all pertinent arguments as they relate to the rejection above, has been addressed.

Prior art made of record but not relied upon in the rejection

Socher et al. (1987) teaches neutralizing antibodies against TNF.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cochrane Carlson, Ph.D., whose telephone number is (703) 308-0034. The Examiner can normally be reached Monday through Thursday from 7:00 A.M. to 4:30 P.M. The Examiner can also be reached on alternate Fridays.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Garnette. D. Draper, can be reached at (703) 308-4232. The fax phone number for Group 180 is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

kcc 5-15-96

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SUPERVISORY PRIMARY EXAMINER
GROUP 1800